REMARKS

Claims 1-22 are pending. Claims 23-25 have been cancelled without prejudice or disclaimer. A "clean" version of the amended portions of the specification and claims is provided above. Amendments are indicated in the section entitled "Version Showing Changes Made" which follows these remarks.

The description of Figure 4 has been amended for clarity. Support is found in the description of the figure (page 4, lines 10-23) and in Figure 4 itself, as originally filed. Applicants submit that this amendment was not necessary, since plots for three different groups are clearly designated in the figure (by symbol) and the description of Figure 4 (by outcome), wherein each group is distinguished by the percent survival at 14 days. However, in the interest of expediting prosecution, the amendments are submitted and entry is respectfully requested.

Priority

The Examiner asserts that the original disclosure (US 09/216,005) is not enabling for the claimed invention, and as such, the previous priority date is lost. The sole reason the Examiner gives to demonstrate a lack of enablement is that working examples and figures have been modified, "therefore, the instant disclosure is not the same as original disclosure, thus the original disclosure is not enabling for the claimed invention." Applicants respectfully traverse, since the two disclosures need not be identical as the Examiner seems to suggest. The form paragraph for such a rejection is:

> ¶ *2.10 Disclosure Must Be the Same*
>
> The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir.1994).

As clearly indicated, the two cases need not be the same; rather, all that is required is that the presently-claimed invention be disclosed in the previous application in compliance with 35 U.S.C. §112.

Applicants respectfully submit that the parent application clearly includes such a disclosure, as it is directed to precisely the same subject matter as the pending case, *i.e.*, extending the survival of a transplant using nucleic acids which modulate heme oxygenase activity in cells. Ample instruction to make and use the presently-claimed invention is found at page 6, line 10 to page 10, line 12 of the parent application, along with a prophetic example of practicing the described method in a heart model. Specifically, the parent specification teaches nucleic acids which function to modulate heme oxygenase activity in cells (page 6, lines 14-22), nucleic acids encode a polypeptide having heme-oxygenase activity (page 6, line 23 to page 7, line 7) and delivery of such nucleic acids page 9, line 3 to page 10, line 12. In addition, a prophetic example provides a step-by-step description of one embodiment of the invention wherein heme-oxygenase encoding nucleic acid is delivered to heart transplants. Subsequent work has shown that contacting heart transplants with a nucleic acid encoding heme oxygenase, as described in the parent application, is effective for extending the survival of the transplant organ (*see* Chaveau et al, Exhibit 16, and Katori et al, Exhibit 17, described in more detail below).

The instant continuation-in-part application incorporates subsequent data obtained in a rat liver model. The Examiner points in particular to these changes in the working examples and in the corresponding figures as indicative of a lack of enablement. Applicants point out that Example 2 of the parent application still appears in the present application as Example 2, it having been merely rewritten for clarity. More importantly, however, working examples are not required for enablement. All that is required is sufficient instruction in the specification for a person of ordinary skill in the art to make and use the invention. The prophetic example provided in the parent case is merely illustrative of the teachings in the detailed description. The working example added to the pending case serves to confirm that the methods disclosed in the parent case would work substantially as described. Moreover, in addition to the liver data, Applicants have also obtained data demonstrating the successful use of the claimed method in a heart model, which further substantiates the prophetic example in the parent, and a kidney transplant model,

which still further substantiates the breadth of the disclosure and the claims.

The Examiner has failed to suggest or describe how the present claimed invention was not disclosed in the previous application. Since the requirement for priority rests on the disclosure of the parent document as a whole and not on whether changes were made in examples or figures that do not alter the scope of disclosure of the current invention, the present application should take priority from the earlier date. Therefore, Applicants respectfully request reconsideration and reinstatement of the original priority date.

Rejections under 35 U.S.C. § 112

Claims 1-14 and 16-22 are rejected under 35 U.S.C. §112, first paragraph, for failing to provide a written description showing that the inventors had possession of the claimed invention. Applicants respectfully traverse.

MPEP § 2163.02 provides several statements regarding the inquiry as to whether the Written Description requirement is satisfied. In one case, the question is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." (*citing: In re Gosteli*, 872 F2d, 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). In another case, the question is whether the specification, "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." (*citing: Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ2d 177, 179 (Fd. Cir. 1985). The MPEP goes on to say that in determining whether the written description requirement is satisfied, "the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed." (MPEP § 2163.02). Applicants submit that the presently claimed invention is so conveyed.

The Office Action asserts that, "In analyzing whether a written description requirement is met for the claimed subject matter as a genus of nucleic acids that modulates HO-1 activity, a representative number of species has to be disclosed by their complete structure..."(page 3, paragraph 3). Claims 1-12 concern a method for extending the survival of an organ transplant, comprising contacting the cells of the transplant with nucleic acids that modulate heme oxygenase activity in said cells, which is specifically defined on page 25, line 22. Applicants point out that

the claimed invention is directed to a method and not the nucleotide itself, therefore, the Examiner's reference to "the claimed subject matter as a genus of nucleic acids" (page 3 of Office Action) is misplaced. The subject matter is a method of extending the survival of an organ transplant. Applicants have shown that contracting an organ transplant with a nucleic acid that modulates heme oxygenase, such as a nucleic acid encoding heme oxygenase, results in the prolongation of the survival of an organ transplant. The skilled artisan will understand that any nucleic acid which modulates heme oxygenase will have a similar effect.

Applicants also point out that the written description requirement is separate and distinct from the enablement requirement. To quote MPEP § 2161, "An invention may be described without the disclosure being enabling (e.g., a chemical composition for which there is no disclosed or apparent method for making) . . . ." Furthermore, nucleic acids to be utilized in the present invention are fully described in the specification so that an ordinary skilled artisan can readily identify the components necessary to practice the claimed methods. (*see* p5, lines 10-17; pp25-26, lines 22-2 for a general description and pp20-21 line 24-6; pp5-6, line 25-2 for routine assays of HO-1 activity). Similar disclosure can be found in the parent application at page 6, lines 14-22; page 8, line 26 to page 9, line 2; and page 7, lines 1-7. However, while the example utilizes HO-1 protein modulators, which are well described in the specification, this is not what is claimed.

In regards to claims 2, 3, and 4, the Office Action asserts that these claims, while drawn to nucleic acids encoding HO-1, do not further limit the claims since they do not describe "modulators of HO-1". Claim 2 and dependent claims 3 and 4 concern a method according to claim 1 wherein the nucleic acid employed has HO-1 activity. We would direct the Examiner's attention to Claim 1's actual wording, "...with a nucleic acid that modulates heme oxygenase-I activity in said cells..." We would remind the Examiner that the claim is not directed to "modulators of HO-I", rather it is directed to a method or extending the survival of an organ transplant employing "modulators of HO-I activity in said cells". Again, the Examiner is directed to page 5, lines 10-17, wherein nucleic acids that function to modulate heme oxygenase activity in cells are generally described. Thus, in the language of the claim, HO-I itself is a modulator of HO-I activity in cells. As such, since the characteristics of HO-I and its antisense nucleotide

are disclosed in the present application and are well known in the art, the present description is sufficient to demonstrate possession.

Additionally, the examples of modulators of HO-I activity in the detailed description provide sufficient description of the nucleic acids that can modulate the HO-I activity in cells. Not only is the addition of nucleic acids encoding HO-I activity-possessing proteins described (p5, line 10-17; pp25-26, lines 22-2) but antisense oligonucleotides derived from the given sequence (SEQ ID: 1) are also described (p5, line 14-17). Additionally, methods are described by which one can routinely test for HO-I activity (pp20-21 line 24-6; pp5-6, line 25-2). As the Examiner is no doubt aware, manipulations which are routine in the art need not, and preferably, should not, be included in the application. (MPEP 2164.01--"A patent need not teach, and preferably omits, what is well known in the art." *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir.1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*,802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denie*d, 480 U.S. 947 (1987)). Identification of nucleic acids useful in the claimed methods is well within the skill of the ordinary artisan and more than a description of the criteria that the nucleic acids must meet, based on routine assays in the art, is not required.

Regarding claims 3, 13, and 14, the Office Action asserts that these claims "are drawn to a group of nucleic acids having HO-1 activity or having at least 80% sequence identity to nucleotides 81-944 of SEQ ID NO:1 and having the biological activity of human HO-1". The Examiner proceed s to suggest that "80% sequence identity" is not enough to show to the skilled artisan that the inventor had possession of the invention as a whole. The Office Action then supports this statement with a quote from the *Encyclopedia Britannica online* and a sentence from a 1976 article concerning peptides (Rudinger, "Characteristics of the amino acids as components of a peptide hormone sequence", In Peptide Hormones (Parsons, ed.), University Park Press, Baltimore, MD (1976) pp.1-7). Once again, Applicants stress that the claims are directed to methods; nucleic acids are not claimed. Only nucleic acids that satisfy the recited criteria are useful in the claimed invention. And, the skilled artisan will readily be able to identify nucleic acids that satisfy the criteria of the claims. Furthermore, in the last quarter of a century (i.e., in the time between Rudinger's writing and the present application) , the very subject that the Office

Action asserts as impossible has become relatively common place in the art. Two completely new fields of science, genomics and proteomics, rely on precisely the same information that the examiner claims would be insufficient to put one on notice of possession of the invention.

In addition, we would direct the Examiner's attention to the literal wording of claims 3, 13, and 14 to point out that the nucleotides themselves are not being claimed, only a method of using said nucleotides is being claimed. Applicants have clearly described a method for extending the survival of an organ transplant by contacting it with a nucleic acid 80% identical to the coding region of SEQ ID NO:1 and encoding a peptide having heme oxygenase activity. Applicants again point out that the written description requirement is separate and distinct from the enablement requirement, and that, "An invention may be described without the disclosure being enabling (e.g., a chemical composition for which there is no disclosed or apparent method for making)...." (MPEP §2161). The skilled artisan will understand from the specification that the critical characteristic for a nucleic acid to be useful in the claimed methods is that it modulate heme oxygenase activity.

Applicants remind the Examiner that the standard for compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed" (*see* MPEP 2163.02). Applicants submit that one of ordinary skill in the art would readily recognize what is meant by "has at least about 80% sequence identity" to a disclosed nucleotide sequence, based on the present disclosure. First, the Examiner is directed to page 6, lines 22-31, wherein the terminology of the claim is literally used. Given the disclosed sequence and general knowledge in the art, a skilled artisan would know what nucleic acid sequences are encompassed by this phrase. However, the specification proceeds to define "percent sequence identity" from page 7, line 3 to page 8, line 20. The WU-BLAST-2 program, described in the specification, is a very common tool used in the art to determine percent identity of nucleic acid and amino acid sequences. The specification provides all of the necessary parameter settings to identify all nucleic acid sequences which fall within the scope of "80% sequence identity" to the disclosed sequence.

Contrary to what is claimed in the 1976 reference cited by the Office Action, the significance of "particular amino acids and sequences for different aspects of biological

activity..." can be determined *a priori* via *in silico* techniques with reasonable confidence. Additionally, it is recognized in the art that many changes of amino acids have absolutely no apparent effect on the protein's global structure or function (Bowie et al., Science, 247:1306-1310 (1990), p1306, right column first full paragraph (Exhibit 1)).

Additionally, the Office Action asserts that the structures and thus functions of the possible proteins could not be determined by one skilled in the art. However, evidence from the field of crystallography is in stark disagreement with this assertion. In general, homologous proteins have similar sequences, structures, and, often function; thus, protein 3D structures can be predicted based on comparison to the structures of known homologues (Alberts et al., Molecular biology of the cell 3rd edition, Garland Publishing (1994), p123, second full paragraph (Exhibit 2)). More particularly, when two sequences share 50% amino acid identity, the relative mean square deviation of their alpha-carbon coordinates is expected to be around 1Å. As such, an accurate model can be predicted for a novel sequence with at least 30% identity with a protein of known structure (Bentz et al., Bioinformatics 15:309-316 (1999) (Exhibit 3) referring to the state of the prior art, in particular: Bajorath et al. Protein Sci., 2:1798-1810 (1993); and Chothia and Lesk EMBO J. 5:823-826 (1986)).

Indeed, the sufficiency of describing a protein in such a manner is not only recognized by the general fields of crystallography, genomics, and proteomics, but is also recognized by the United States Government, as demonstrated by the NCBI website: http://www.ncbi.nlm.nih.gov. The NCBI states as two of its purposes to, "[1]conduct[] research in computational biology, [and] [2] develop software tools for analyzing genome data..." It is precisely these standard and well known tools and techniques in computational biology that the current application is employing in defining nucleic acids useful in the present invention. In other words, computational biology and the analysis of genomes fundamentally rely upon descriptions of sequences, not by a literal comparison, but by comparison by homology. The Applicants would draw the Examiner's attention to the fact that the National Institute of Health recognizes such a description of a protein (i.e. 80% sequence homology) as a standard manner for identifying and describing nucleic acids, and indeed, promotes such characterization by the use of programs such as BLAST, PSI-BLAST, PHI-BLAST, and RPS-BLAST on its website, all of which function solely to do these exact

comparisons.

In rejecting the claims, the Office Action contends that specific embodiments may be inoperable. Even assuming *arguendo* that specific embodiments are inoperable, the M.P.E.P. § 2164.08 states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

The Examiners statement is based on the erroneous assumption that what is claimed are the nucleic acids, while Applicants have repeatedly pointed out that this is not the case. The claims only encompass methods wherein a nucleic acid which modulates heme oxygenase is utilized. While the skilled artisan could readily determine whether a nucleic acid has such activity with the expenditure of no more effort than is normally required in the art by techniques described in the application (pp20-21 line 24-6; pp5-6, line 25-2), the claims do not encompass methods utilizing nucleic acids that lack such activity. Therefore, the rejection does not address the true subject matter of the claims.

As a final consideration, due to the highly malleable nature of protein design, we would respectfully direct the Examiner to In re Goffe, 191 USPQ 429 (CCPA 1976) where the Court of Customs and Patent Appeals stated:

> "to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts". (Emphasis supplied).

Considering that homology can be used, not only to engineer the properties and structure of a protein, but also as a method to characterize and identify proteins in computational analysis, Applicants suggest that the use of homology to describe a protein should be sufficient to allow one skilled in the art to recognize the invention by standard techniques in the field (i.e. BLAST on the NCBI webpage). Additionally, the fact that without the use of homology, no effective

protection could be given to any protein or nucleic acid suggests that the rejection of homology in general to define a claim is misplaced.

In light of the discussion above, Applicants submit that claims 1-14 and 16-22 satisfy the written description requirements of 35 U.S.C. §112, first paragraph. As such, the Applicants respectfully request that the rejection be withdrawn.

Claims 1-22 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully traverse.

The test of enablement is whether a person of ordinary skill in the art can make and use the claimed invention without undue experimentation. Applicants submit that the specification, along with the general knowledge in the field, provides ample instruction for the skilled artisan to make and use the invention without undue experimentation.

The Office Action states that while the specification may be sufficient to establish enablement for "preservation of cell morphology in an *ex vivo* liver perfusion model", it is not sufficient to enable extending the survival of "any organ, any type of transplant, in any recipient." Additionally, the Office Action asserts that gene therapy itself is not enabled. As will be apparent from the citations below, at the time of filing, the treatment with gene therapy of many different organs resulting in expression to create the presently desired result was well known in the art at the time of filing.

As a preliminary matter, Applicants question the Examiner's characterization of the results described in Example 3. Not only did Applicants show prolonged survival of recipients with HO-1 nucleic acid-treated transplants, but function of treated transplant livers was improved (*se* page 31, line 29 to page 32, line 4) and hepatocyte damage and bile duct proliferation was reduced (page 32, line 5). These data show that the transplanted organs, themselves, faired better under treatment, not just the recipients.

Applicants submit that the best measure of what constitutes enablement for gene therapy applications, with regard to patentability, is the PTO itself. Applicants submit that at the time of filing, fully enabled methods of gene therapy, in which the present invention would be useful,

were in the hands of the skilled artisan. For example, the Examiner's attention is directed to the claims of USPN 5,912,236, directed to a method of treating a tumor by introducing a vector (Claim 1), which may be a plasmid (i.e., a nucleic acid; Claim 10), *in vivo* (Claim 14). These methods were in the hands of the skilled artisan by at least March 5, 1996, upon issuance of the parent application, and fully enabled at the time of its priority date in 1993. USPN 5,599,712 (issued 2/4/1997) claims a method of gene therapy involving administering polynucleotide to a subject *in vivo* (Claim 1). And, USPN 5,705,151 (issued January 6, 1998) claims a method of treating a mammal having cancer by administering to the mammal a composition comprising a recombinant construct (nucleic acid) (Claims 1 and 2). Clearly, gene therapy was sufficiently predictable to be patentably enabled at the time of filing the present application.

In addition to the PTO's decisions, there was sufficient prior art concerning gene therapy so as to make it routine at the time of filing of this application. As a first example of the state of the relevant art, Applicants submit Boasquavisque et al., *J. Thorac. Cardiovasc. Surg.* 115(a):38-44 (1998) (Exhibit 4), which describes *ex vivo* transfection of grafts of plasmids which may be made, as in the present invention, using a commercially available liposome preparation using well-known techniques. An *in vivo* example of effective gene therapy is found in Nakamura et al., *Gene Therapy* 5:1165-1170 (1998) (Exhibit 5), resulting in expression of the desired protein and marked physiological effect. Another example of gene therapy in vivo is found in Lee et al., *Ann. Thoracic Surg.* 66(3):903-907 (1998) (Exhibit 6) involving treatment of the lungs.

A review by Templeton and Lasic (*Molec. Biol.* 11(2):175-180 (April, 1999)) (Exhibit 7) is submitted as a more accurate statement of the state of the art regarding liposome delivery methods. Although it was published after the priority date of the present application, all of the references that it cites in support of its disclosure predate the priority date. In general, it teaches that the problems discussed in Orkin et al., (NIH Report, 1995 Dec.), as cited in the Office Action, have been overcome or diminished by advances made subsequent to the earlier references. The state of the art at the time of filing of the present application was such that a skilled artisan could routinely perform gene therapy in a graft tissue by *ex vivo* or *in vivo* administration without undue experimentation.

The Office Action cites Levine et al. (Mole Med Today 1999 Apr 5:165-171) and Boucher

et al (J Clinical Invest 1999 Feb; 103:441-5) for indications of limitations in gene therapy. applicants first point out that, while there may still be hurdles to the widespread commercial use of gene therapy in all of its hope-for incarnations, that does not render all applications of gene therapy not enabled. Each of these paper refers to specific disease states, neither of which are related to the present methods of extending organ transplant survival. As such, these references are not on point. It is true that the wide-spread commercial exploitation of gene therapy may require further developmental work; however, this is not the standard of patentability. The applicant points out that commercial exploitation of gene therapy requires many different considerations than the patenting of gene therapy techniques; the standards are quite different. Certainly the Examiner will appreciate that a new protein may be patentable although methods for its large scale production, sufficient to allow its wide-spread use, have not been developed. The standard for 35 U.S.C. §112 enablement is that one skilled in the art can make and use the invention without undue experimentation.

The present specification teaches the delivery of nucleic acids encoding heme oxygenase to cells of an organ transplant by viral-mediated transfer (*see* page 21, line 25 to page 22, line 11). Muruve et al., *Transplantation* 64(3):542-546 (1997) (Exhibit 8) describes the *ex vivo* delivery of nucleic acid to transplanted organs. McClane et al., *Human Gene Ther.* 8:739-746 (1997) (Exhibit 9) show that direct injection of adenovirus into the pancreas provides for expression of the protein introduced in the transfecting nucleic acid in over 60% of pancreas cells. Brauner et al., *J. Thorac. Cardiovasc. Surg.* 114:923-933 (1997) (Exhibit 10) describes extension of cardiac allograft survival after *ex vivo* perfusion of graft hearts with adenoviral vectors encoding two different cytokines.

Additionally, in rejecting the claims, the Office Action contends that specific embodiments may be inoperable. Even assuming *arguendo* that specific embodiments are inoperable, the M.P.E.P. § 2164.08 states:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569,

1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

In view of this requirement and the large number of embodiments enabled by the specification, the possibility that specific embodiments of the current application may be inoperative is an improper basis for a rejection under §112, first paragraph. Furthermore, Applicants respectfully assert that a skilled artisan could determine inoperable embodiments, if any, with the expenditure of no more effort than is normally required in the art by techniques described in the application (pp20-21 line 24-6; pp5-6, line 25-2).

As can be seen from the above-cited references, one of ordinary skill had ample means at his/her disposal at the time the present application was filed to deliver to and express in an organ graft a nucleic acid of their choice. The real barrier to effective gene therapy was, and still is, identification of substances that may be delivered by gene therapy techniques to obtain a desired result. In the present case, Applicants have provided such a substance in the protein heme oxygenase.

Additionally, the Office Action asserts that an animal model is inadequate to allow extrapolation to human treatment. The test of sufficiency of models, both *in vitro* and *in vivo*, is whether one of ordinary skill in the art would accept the model as reasonably correlating to the condition of which it is a model. (*See* MPEP § 2164.02).

The Office Action suggests two references, Orkin et al. and Levine et al. which suggest the possibility of a possible problem extrapolating results from animal models in particular disease models: CF and HIV. These diseases are put in contrast to most disease models. Applicants remind the Examiner that consideration of any reference should be made as a whole. While Orkin et al. did mention possible problems, it was in no way a criticism of animal models for human diseases. For instance, on page 1, Item 4 (last full paragraph), Orkin et al. states that the effective design of therapeutic approaches can be carried out in appropriate animal models. Indeed, the section entitled "Animal Models of Disease" starts with: "Principles of disease pathogenesis and the development of gene therapy approaches can often be addressed by studying animal models of human disease." Then it continues, "Despite potential phenotypic differences between human patients and animal models of disease, the study of animal models for the design

of gene therapy approaches in a preclinical setting is important and should not be undervalued."

The Examiner cites Boucher et al. as evidence of the problems of gene therapy. This reference is directed solely to the issue of gene therapy of CF, a disease that the field recognizes as being particularly difficult for gene transfer. (see Orkin et al.) The problem with gene therapy for CF (as identified in Boucher et al.) is primarily due to inefficient gene transfer through the airway epithelia cells. The identified reason for the inefficient transfer is the "extremely effective adaptations of airway epithelia", something that is not a problem of gene transfer in general. Boucher et al.'s proposed solution involved loosening the external tight gap junctions to allow access to the internal section of the cells, it is important to note that in transplanted organs, internal access is always available for perfusion of a solution, thus, such an issue wouldn't be a problem in the current application since one would have access to the internal side of the organ.

In further rebuttal to the rejection, Applicants submit abstracts from 1997 (the year before the filing of the present application), 1998, 1999 and 2000 publications which show that the rodent allograft model was, at the time of filing, and continues to be considered by those of skill in the art to be reasonably correlated to the condition (e.g., human organ transplantation) of which it is a model. Each of Schuler et al., *Transplantation*, 64(1):36-42 (1997) (Exhibit 11), DeBruyne et al., *Gene Ther.* 5(8):1079-1087 (1998) (Exhibit 12), Weringer et al., *Transplantation* 67(6):808-816 (1999) (Exhibit 13) and Moffatt et al., *Transplantation*, 69(8):1724-1726 (2000) (Exhibit 14) teach that the rodent heart allograft model is not only a useful tool for studying organ transplantation, but is generally considered clinically relevant. The references are only exemplary. The rodent allograft model continues to be widely used and accepted as a cost effective and telling tool for identifying clinically useful drugs for transplantation.

In further support of the enablement of the present specification, both in terms of gene therapy and the effective scope of different forms of transplants, applicants submit several reports published subsequent to filing of the application which show the viability of the claimed invention as specifically taught in the present disclosure. While the references were published after the filing date of the present application, the applicants are not using subsequent work to supplement the disclosure of the application; rather, the subsequent work is presented to show that the utility asserted and shown in the application is supported by further research, and that the

specification fully enables therapeutic use of gene therapy in extending the survival of organ transplants. MPEP 2164.05(A). *See* In re Wilson, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 2d 1063 (BPAI 1993); Gould v. Quigg, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative."

In addition to the application's working example of extending the survival of liver transplants, the claimed methods, using the teaching of the present disclosure, have been shown to extend survival of: kidney isografts (*see* Blydt-Hansen, Transplant, May 11-16, 2001; Exhibit 15) and heart allogenic transplants (*see* Chauveau et al., Transplant, May 11-16; Exhibit 16 and Katori et al., Transplant, May 11-16; Exhibit 17). Amelioration of well recognized signs of acute rejection in liver grafts using the present techniques has also been shown (*see* Ke et al., Transplant, May 11-16; Exhibit 18). Applicants also note that the effectiveness of *ex vivo* administration (i.e., direct application of the nucleic acid vector to the harvested transplant organ) was similar to administration to the donor, as described in the present specification. These reports should allay the Examiner's concern that the current invention does not enable transplants of other organs or require procedures not typically available in a clinical setting.

The present invention discloses a method for extending the survival of an organ transplant in a recipient by contacting cells of the transplant with nucleic acid that modulated heme oxygenase activity in a cell, thereby extending the survival time of the transplant. These examples discussed above show that the method is not limited by the type of transplant, the type of organ being transplanted, or the organism receiving the transplant. Additionally, the PTO itself has recognized gene therapy as enabled.

For the reasons discussed above, Applicants submit that the present disclosure satisfies the enablement requirements of 35 U.S.C. § 112, first paragraph for Claims 1-22. Therefore, Applicants respectfully request the withdrawal of this rejection.

Rejection under 35 U.S.C. § 102

Claims 23-25 are rejected under 35 U.S.C. §102(b) as being anticipated by Abraham et al., *Int. J. Molec. Med.* 1:657-663 (1998). Applicants first submit that this reference may not be used as 102(b) art because it does not predate the filing of the priority application by more than one year. As discussed above, the presently claimed invention is fully supported by the parent application. The present rejection is moot in light of the cancellation of claims 23-25. However, as stated, these claims have been cancelled without prejudice, disclaimer or admission. Applicants reserve the right to address this rejection, should claims relating to the subject matter of Claims 23-25 be re-introduced in the present application or a entered in a subsequent application.

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date Oct. 1, 2001

James J. Diehl
Reg. No. 47,527 for
Todd A. Lorenz
Reg. No. 39,754

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

VERSION SHOWING CHANGES MADE

In the Specification:

The paragraph beginning at page 4, line 18 has been amended as follows:

Figure 4 shows results demonstrating prolongation of liver isograft survival. Lean Zucker rats served as recipients of liver transplants from obese Zucker donors. Donor rats were either pretreated with CoPP or Ad-HO-1 or remained untreated before liver procurement followed by 4 hours of cold ischemia. Control animal survival at 14 days was 40% (◆) versus 80% (■) and 81.8% (▲) in the CoPP and the Ad-HO-1 group, respectively (n = 10–11 rats/group).

In the Claims:

Claims 23-25 have been cancelled without prejudice, disclaimer or admission.